Universidade de Aveiro Escola Superior de Saúde

2014

Nádia Patrícia Duarte de Almeida

Impacto do exercício isodinâmico reproduzindo uma atividade da vida diária na rigidez arterial em indivíduos com hipertensão resistente

Impact of isodynamic exercise reproducing a daily living task on arterial stiffness of subjetcs with resistant hypertension

Universidade de Aveiro Escola Superior de Saúde

2014

Nádia Patrícia Duarte de Almeida

Impact of isodynamic exercise reproducing a daily living task on arterial stiffness of subjects with resistant hypertension

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Fisioterapia, realizada sob a orientação científica do Professor Doutor Fernando Ribeiro, Professor adjunto da Escola Superior de Saúde da Universidade de Aveiro, e coorientação do Professor Doutor José Mesquita Bastos, Professor adjunto convidado da Escola Superior de Saúde da Universidade de Aveiro

O Júri

Presidente	Prof. Doutora Anabela Gonçalves da Silva Professora adjunta da Escola Superior de Saúde da Universidade de Aveiro
Arguente	Prof. Doutor Alberto Jorge Carvalho Alves Professor coordenador do Instituto Superior de Ciências Educativas de Felgueiras
Orientador	Prof. Doutor Fernando Manuel Tavares da Silva Ribeiro Professor adjunto da Escola Superior de Saúde da Universidade de Aveiro

Agradecimentos

Ao meu orientador Prof. Dr. Fernando Ribeiro, por toda a ajuda, compreensão e motivação dada ao longo do estudo.

Ao Prof. Dr. Mesquita Bastos e toda a equipa, que permitiram e contribuiram para a realização deste estudo.

Aos meus colegas do Mestrado em Fisioterapia, a quem agradeço a partilha de conhecimentos, o que possibilitou um desenvolvimento professional e pessoal.

Aos meus amigos, em especial à Diana Gomes, pelo apoio e por todas as palavras de incentivo.

À minha família, pela presença e carinho incondicionais.

A todas as pessoas que estiveram presentes nesta caminhada, agradeço todo o apoio, amor e compreensão.

Palavras-chave Rigidez arterial, hipertensão resistente, exercício isodinâmico

Resumo

Introdução e objetivos: A hipertensão resistente é uma condição importante, cuja relação com o exercício permanece ainda pouco estudada. Um dos principais contribuintes para a hipertensão é a rigidez arterial, sendo assim um preditor importante das doenças cardiovasculares. O presente estudo examinou os efeitos de uma caminhada na passadeira com e sem carga na rigidez arterial, em medidas derivadas de pressão central e no índice de aumentação, em doentes com hipertensão resistente.

Metodologia: Foram estudados vinte pacientes voluntários, com hipertensão resistente. Os indivíduos foram divididos aleatoriamente em dois grupos. Os participantes de um dos grupos caminharam durante 10 minutos numa passadeira a uma velocidade de 5Km/h, sem transportarem carga adicional. Os do outro grupo caminharam durante o mesmo tempo e à mesma velocidade, carregando uma carga adicional de 10% do seu peso corporal em dois garrafões de água com alça, dividido em ambos os membros superiores. Foi realizada a análise da onda de pulso radial e da velocidade da onda de pulso em repouso e imediatamente após o exercício, utilizando tonometria de aplanação.

Resultados: O estudo demonstrou que caminhar numa passadeira, com ou sem carga, não altera o índice de aumentação a 75bpm nem a velocidade da onda de pulso. A pressão sistólica arterial (variação no grupo sem carga foi de -7.2 ± 2.9 mmHg vs no grupo com carga adicional de -13.3 ± 14.9mmHg, $p<0.05$), a pressão de pulso (variação no grupo sem carga foi de -21.4 ± 13.4mmHg vs no grupo com carga adicional de -20.9 ± 17.6, $p<0.05$) e a pressão de pulso aórtica (variação no grupo sem carga foi -19.6 ± 13.9 vs no grupo com carga adicional de -14.4 ± 13.3mmHg, $p<0.05$) aumentaram significativamente em ambos os grupos, após o protocolo de exercício. Por outro lado a pressão arterial diastólica (variação no grupo sem carga foi de 13.2 ± 11.3mmHg vs no grupo com carga adicional de 9.7 ± 12.5mmHg, $p<0.05$) diminuiu significativamente em ambos os grupos, após o protocolo de exercício. A alteração nestes parâmetros não foi significativamente diferente entre os grupos.

Conclusão: Em pacientes com hipertensão resistente, caminhar com carga adicional de 10% do peso corporal (exercício aeróbio acompanhado por contração isométrica dos membros superiores) não altera a rigidez arterial.

Key words

Arterial stiffness, resistant hypertension, isodynamic exercise

Abstract

Introduction and objectives: Resistant hypertension is an important condition whose relationship with the exercise remains little studied. A major contributor to hypertension is arterial stiffness, thus it is an important predictor of cardiovascular disease. This study examined the effects of walking on the treadmill with and without load in arterial stiffness in pulse wave velocity, derived measures of central pressure and augmentation index in patients with resistant hypertension.

Methodology: Twenty patients with resistant hypertension were studied. Subjects were randomly divided into two groups. The participants of one of the groups walked for 10 minutes on a treadmill at a speed of 5Km/h without additional load. The other group walked the same time and at the same speed carrying an additional load of 10% of their body weight, in two water carboys with handle, divided into both upper limbs. The analysis of the radial pulse wave and the speed of wave pulse were performed at rest and immediately after exercise, using applanation tonometry.

Results: The main result indicates that walking with and without load carriage does not change augmentation index at 75bpm and pulse wave velocity. The systolic blood pressure (SBP) (change in group without load -7.2 ± 2.9mmHg vs. group extra-load -13.3 ± 14.9mmHg, $p<0.05$), the pulse pressure (PP) (change in group without load -21.4 ± 13.4mmHg vs. group extra-load -20.9 ± 17.6mmHg, $p<0.05$) and aortic pulse pressure (APP) (change in group without load -19.6 ± 13.9mmHg vs. group extra-load -14.4 ± 13.3mmHg, $p<0.05$) increased significantly in both groups after the exercise protocol; on the other hand diastolic blood pressure (change in group without load 13.2 ± 11.3mmHg vs. group extra-load 9.7 ± 12.5mmHg, $p<0.05$) decreased significantly also in both groups after the exercise protocol. The changes in these parameters were not significantly different between groups.

Conclusions: In patients with resistant hypertension, walking with additional load of 10% of their body weight (aerobic exercise accompanied by isometric contraction of the upper limbs) does no alter arterial stiffness.

INDEX

TABLE INDEX

FIGURES INDEX

ABBREVIATIONS

AIx	Augmentation index
AIx@75	AIx at a HR of 75 beats per min
AS	Arterial Stiffness
APP	Aortic pulse pressure
BP	Blood pressure
CVD	Cardiovascular diseases
CBP	Central blood pressure
DBP	Diastolic blood pressure
HR	Heart rate
PBP	Peripheral blood pressure
PP	Pulse pressure
PWV	Pulse wave velocity
RH	Resistant hypertension
SBP	Systolic blood pressure

CHAPTER 1 – INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death worlwide, representing 31% of all global deaths (WHO, 2011). In Portugal the numbers are also alarming, with 37% of deaths caused by CVD (WHO, 2013). Hypertension (HT) is one of the most important risk factors for CVD, 45,6% of Portuguese people are hypertensive and 5-10% of them have not their blood pressure (BP) controlled (Cortez-Dias, Susana Martins, Adriana Belo, 2009; S. Paiva, Complementar, & Geral, 2005). When BP is ≥140/90 mm Hg (or <130/80 mm Hg in patients with diabetes mellitus or chronic kidney disease) in spite of concurrent use of 3 antihypertensive agents of different classes in adequate doses including a diuretic or a BP that is controlled with ≥4 antihypertensive agents, it is called resistant hypertension (Carey, 2013). Patients with resistant hypertension are at high risk for adverse cardiovascular events (Dimeo et al., 2012).

The most contributor to hypertension is the arterial stiffness and so a potent predictor of CVD (Sakuragi & Abhayaratna, 2010). Arterial stiffness is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall (Cavalcante, Lima, Redheuil, & Al-Mallah, 2011). These induce several harmful hemodynamic consequences including increases in systolic blood pressure and pulse pressure, which are related to systolic and diastolic cardiac dysfunction at a central level, augmented cardiac load and reduced coronary perfusion (Cecelja & Chowienczyk, 2012).

Large central elastic arteries, such as aorta, are a low-resistance conduit and act as a cushion of flow pulsations. With an increase of arterial stiffness there is an increase in systolic blood pressure (SBP) because the cushing function to accommodate the systolic volume ejected by the left ventricle cannot be performed without a significant increase in peak BP (Lydakis et al., 2008). The pressure wave form recorded in arterial tree is the junction of ejection waves and reflected waves. When arteries are compliant and elastic, the reflected wave merges with the ejection wave in the late systolic or diastolic phase and there is a little or no effect on central SBP. On the other hand, when the arterial stiffness increases, pulse wave velocity (PWV) increases too, resulting in earlier return of the wave in the systolic phase, thus augmenting the central SBP and left ventricular afterload. The increase of pressure relative to reflected wave determines augmentation index (AIx), which in turn reflects the excessive load on the left ventricle due to reflection of waves. It has been demonstrated that AIx derived from peripheral arterial tonometry correlates with cardiac risk factors and coronary

artery disease; it may be a useful measure of assessing overall risk for coronary artery disease (Patvardhan et al., 2011).

Given this close relationship between AS and CVD, several nonpharmacological interventions to reduce arterial stiffness are currently being investigated, one of the most important is exercise training (Mancia et al., 2013). Some studies in healthy subjects, showed that regular aerobic exercise has a beneficial effect on arterial stiffness, whereas resistance training may have an unfavourable influence on central haemodynamics (Cecelja & Chowienczyk, 2012; Lydakis et al., 2008). In cardiovascular disease patients, a single bout of aerobic exercise of moderate intensity increased proximal arterial stiffness rising carotid systolic BP, pulse pressure and pulse pressure amplification (Tartière-Kesri, Tartière, Logeart, Beauvais, & Cohen Solal, 2012).

Per opposition to the acute effects of aerobic exercise on arterial stiffness, less is known about the repercussions of isodynamic exercise. This is a topic of particular interest considering that numerous daily living activities include isodynamic exercise, which combines dynamic and isometric muscle actions, such as walking with backpack carriage or with hand load carriage.

PURPOSE

In cardiac rehabilitation, oftentimes, physiotherapists advice walking, incorporating it into daily living tasks. Due to the lack of definite data regarding this particular kind of exercise this study analyzed subjects with resistant hypertension, which in general have already increased arterial stiffness at rest and are at higher risk. Thus, the main purpose of the present study was to assess the effects of treadmill walking with hand load carriage on arterial stiffness, derived measures of central pressure and augmentation index in subjects with resistant hypertension.

CHAPTER 2 – LITERATURE REVIEW

Resistant hypertension is a health problem that has been increasingly studied in the last years due to its importance for CVD risk (Carey, 2013; Kumar, Calhoun, & Dudenbostel, 2013; Rourke, Staessen, Vlachopoulos, Duprez, & Plante, 2010). Arterial stiffness emerges as a very powerful predictor for CVD (Cecelja & Chowienczyk, 2012). The acute effects of aerobic exercise on the stiffness of arteries are well defined, however less is known about isometric and isodynamic exercise (Lydakis et al., 2008; Tartière-Kesri et al., 2012). This chapter addresses the issue of resistant hypertension, arterial stiffness and how it is measured and the acute effects of exercise on arterial stiffness.

2.1 Resistant hypertension

Hypertension is one of the leading risk factors influencing the global burden of CVD, resulting in increased incidence of all-cause and cardiovascular mortality, coronary heart disease, sudden death, stroke, heart failure, atrial fibrillation, peripheral artery disease, and renal insufficiency (Fagard, 2012). It is estimated that hypertension lead to over 7 million deaths each year that is about 13% of the total number of deaths worldwide. Despite lifestyle changes, antihypertensive drug treatment and combinations of drugs on the management of hypertension, it remains inadequately controlled in many patients and a number of them are considered to have resistant hypertension (Fagard, 2012).

Resistant hypertension is defined as the inability to achieve goal BP ≥140/90 mm Hg (or <130/80 mm Hg in patients with diabetes mellitus or chronic kidney disease) in spite of concurrent use of 3 antihypertensive agents of different classes in adequate doses including a diuretic or a BP that is controlled with ≥4 antihypertensive agents (Carey, 2013).

Although the number of failed antihypertensive drugs required for the classification of resistant hypertension is arbitrary, it is defined in order to identify patients who are at high risk of having reversible causes of hypertension and/or patients who, because of persistently high BP levels, may benefit from special diagnostic and therapeutic considerations (Calhoun et al., 2008; Carey, 2013).

Since the publication of the American Heart Association (AHA) Scientific Statement on the Evaluation and Treatment of Resistant Hypertension in 2008, several studies have pointed out that resistant hypertension has an incidence rate of 1.9% in 200 000 patients (Pimenta &

Calhoun, 2012). The prevalence of resistant hypertension has been a matter of debate. The exact prevalence of resistant hypertension is not known, it is derived from cross-sectional studies and post-hoc analyses of clinical trial and is estimated at 10%- 35% of all patients being treated for hypertension (Kumar et al., 2013).

According to the European arterial hypertension guidelines (2013) a correct diagnostic approach to resistant hypertension requires detailed information on the patient's history to not be confounded with uncontrolled hypertension, which involves patients who are not at goal with fewer than 3 drugs, or with inadequate treatment regime. Pseudoresistant hypertension arises from a wrong diagnosis because of poor BP assessment technique, poor adherence and a possible white coat effect (Kumar et al., 2013).

Resistant hypertension may have many causes including (i) lifestyle factors such as obesity or large weight gains, excessive alcohol consumption and high sodium intake, which may oppose the BP-lowering effect of antihypertensive drugs via systemic vasoconstriction, sodium and water retention and, for obesity, the sympatho-stimulating effect of insulin resistance and increased insulin levels; (ii) chronic intake of vasopressor or sodium-retaining substances; (iii) obstructive sleep apnoea (usually but not invariably associated with obesity), possibly because nocturnal hypoxia, chemoreceptor stimulation and sleep deprivation may have a long-lasting vasoconstrictor effect; (iv) undetected secondary forms of hypertension and (v) advanced and irreversible organ damage, particularly when it involves renal function or leads to a marked increase in arteriolar wall-lumen ratio or reduction of large artery distensibility (Calhoun et al., 2008; Mancia et al., 2013; L. Paiva et al., 2012).

Patients with resistant hypertension should be monitored closely. They have higher rates of death, myocardial infarction, congestive heart failure, stroke and chronic kidney disease compared with those having controlled hypertension (Kumar et al., 2013).

2.2 Arterial stiffness

The function of arteries is the transport of the blood to the tissues, under pressure. Arteries are divided into two anatomic regions with distinct functions: (1) large elastic arteries (e.g. aorta, carotid, iliac) and (2) muscular arteries, especially those in lower body (e.g. femoral, popliteal, posterior tibial), that alter their tone and consequently change the speed of travel of the pressure wave along their length, thereby determining the extent to which and timing at which, the reflected wave arrives back at the heart (Gkaliagkousi & Douma, 2009).

Arteries have resistant vessel walls and blood rapidly flowing in them. The arterial wall is divided into three layers: intima, media and adventitia. The first layer is comprised by a single layer of endothelial cells, insured by smooth muscle cells and is separated from the media by the internal elastic lamina, which is composed largely of elastic fibers. The middle layer is the most affected by arterial stiffness due to its nature. It is composed of elastic laminae in concentric layers intersped with collagen and smooth muscle cells. Adventitia consists mainly of fibroblasts and collagen (Gkaliagkousi & Douma, 2009).

After each heartbeat a new wave of blood fills arteries. If the arterial system is not distensible, blood flow would occur only during cardiac systole and there would be no flow during diastole. So, the compliance of the arterial tree reduces pressure pulsations to the almost no pulse when blood reaches the capillaries. That explains why blood flow is mostly continuous with very little pulsation. Pulse pressure is the difference between the SBP, which in a young adult is around 120 mmHg, and DBP (Guyton, A.C. & Hall, 2002). A rise in PP is the major cause of the age-related increase in prevalence of hypertension and has generally been attributed to arterial stiffening (Cecelja & Chowienczyk, 2012).

Arterial stiffness is a generic term that describes the rigidity of the arterial wall, being the inverse of distensibility (Δpressure/Δvolume) (Cecelja & Chowienczyk, 2012; Quinn, Tomlinson, & Cockcroft, 2012). Elasticity of arterial segments is not constant and depends also on its distending pressure. When distending pressure increases there is greater recruitment of inelastic collagen fibers and thereby a reduction in elasticity (Gkaliagkousi & Douma, 2009).

The stiffness of arterial wall has been increasingly studied in recent years and is recognized as an important measure of target organ damage in hypertension and a potent predictor of cardiovascular morbidity and mortality. AS is one of the earliest detectable manifestations of adverse structural and functional changes within the vessel wall (Cavalcante et al., 2011).

The basic mechanisms that lead to arterial stiffness and hypertension are age-related degeneration of elastin fibers and the increase of collagen deposition (Montero, Roche, & Martinez-Rodriguez, 2014; Sakuragi & Abhayaratna, 2010). Moreover, endothelial dysfunction and elevated proinflammatory cytokines, both reported in hypertensive subjects, may promote arterial stiffness through decreased nitric oxide bioavailability, increased endothelin-1 production and stimulation of vascular smooth muscle proliferation (Bautista, 2003). Also worth mentioning that arterial stiffness has been consistently linked to micro-inflammation in the general population, in patients with high cardiovascular risk and

particularly in chronic kidney disease patients (Gusbeth-tatomir & Covic, 2009). Other factors that contribute to arterial stiffness include estrogens deficit, enhanced salt intake, smoking, high levels of homocysteine and diabetes (Kinlay et al., 2001).

The extent to which arterial stiffness is modifiable is still little consensual. The structural degeneration that underlies arterial stiffness in elastic arteries is largely irreversible, while the stiffness in muscular arteries can be attenuated directly by vasodilator therapy and indirectly by improving endothelial function through medical and lifestyle therapy (Sakuragi & Abhayaratna, 2010).

2.1.1 Central blood pressure

High BP is a major risk factor for CVD (Papaioannou, Protogerou, Stamatelopoulos, Vavuranakis, & Stefanadis, 2009). Central blood pressure (CBP) ≥50 mm Hg predicts adverse CVD outcome, independent of age, gender or diabetic state (Roman et al., 2009).

Blood pressure is a principal vital sign, which for many years has been measured at the periphery (e.g. at the brachial artery). However, BP at peripheral arteries does not accurately reflect the level of BP close to the heart such as at the ascending aorta and at the carotid arteries (Papaioannou et al., 2009).

CBP is, physiologically, more relevant to ventricular-vascular coupling compared to peripheral BP (Roman et al., 2009). The term “central” is used to characterize BP that is estimated at central arteries. Thus, CBP corresponds to aorta and carotids arteries pressure (Papaioannou et al., 2009).

Normally, the mean of central SBP increases with age. It is lower in women until the sixty decade of life, and reaches a maximum of 120 ± 8 mmHg in men and 120 ± 1 mmHg in women. Women has higher values of CBP after the fifth decade of life (Nelson et al., 2010).

2.2.2 Pulse wave velocity (PWV) and augmentation index (AIx)

Aortic stiffness can be assessed with a variety of non-invasive methods. The “gold standard” non-invasive measure of aortic wall stiffness, is the carotid- femoral pulse wave velocity, also called aortic pulse wave velocity (PWV) (Laurent et al., 2006).

The PWV is a simple and non-invasive technique that provides information about mechanical properties of the arterial tree, and ventricular-vascular interaction and can also be used to assess endothelial function (Rocha, 2011).

Reference values in the normal adult of middle-age are 4 m/s in the ascending aorta, 5 m/s in the abdominal aorta and carotids, 7 m/s in the brachial artery, and 8 m/s in the iliac arteries (Zambanini et al., 2005).

Arterial stiffness increases PWV resulting in earlier return of the wave in the systolic phase, thus augmenting the central systolic BP and left ventricular afterload. Thus, both parameters have been identified as prognostic indicators of cardiovascular risk. The European Society of Hypertension and The European Society of Cardiology consider that increased carotid-femoral PWV (>10 m/s) is an index of subclinical organ damage in hypertensive patient (Mancia et al., 2013).

Pulse wave is reflected throughout the arterial tree at junctions or sites of different impedance (lying peripheral resistance) returning then to the aorta and the left ventricle. The reflected waves have the same speed as the wave of direct pulse (Hamilton, Lockhart, Quinn, & McVeigh, 2007).

The timing of the reflected wave depends on the elastic properties and the length of the arterial system (Kinlay et al., 2001). Under ideal conditions the wave reaches the aorta during diastole improving coronary perfusion and limiting the transmission of pulsed power to the periphery, which could damage the microcirculation (Hamilton et al., 2007). Thereby, the reflected wave does not interfere with the ejection wave and does not cause increased central SBP. With the increasing of the stiffness of arteries, the pulse wave velocity also increases; the compliance of large vessels decreases, inducing early reduction in vascular diameter, resulting in a decrease of the normal impedance discontinuity. The wave is reflected earlier, reaching the heart during the systole. Thus, joining the wave pulse ejection, causing amplification (Nelson et al., 2010; Sharman, Davies, Jenkins, & Marwick, 2009).

This phenomenon is called Augmentation Index (Aix) which denotes the difference in amplitude between incident (Pi) and reflected (Ppk) pulse waves as a percentage of pulse pressure (Dawson, Black, Pybis, Cable, & Green, 2009; Sakuragi & Abhayaratna, 2010).

Aix is a measure of the contribution that the wave reflection makes to the central arterial pressure waveform. It provides a measure of systemic arterial stiffness because the

amplitude and timing of the reflected wave depends on the stiffness of arterial tree (Lydakis et al., 2008). The Figure 1 describes central pulse waveform analysis, where Ti is the transit time of the pulse wave from the heart to the peripheral reflecting sites and back to the heart. Normally it is used as an indicator of aortic PWV and arterial stiffness because when stiffness increases, PWV also increases and both resulting in shortening of Ti (Lydakis et al., 2008).

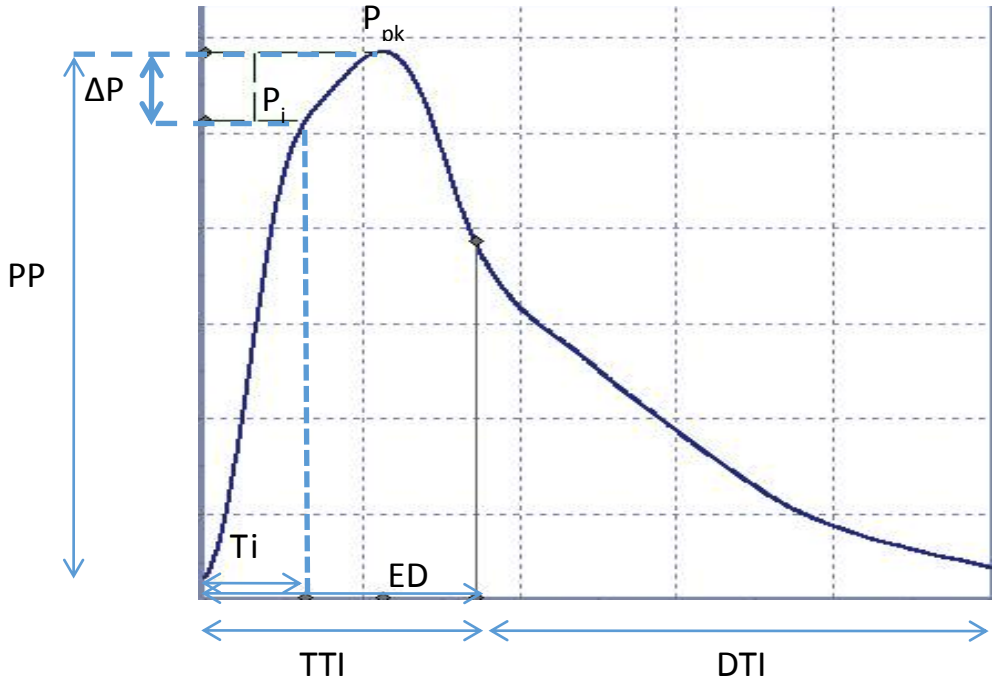

Figure 1-Central pulse waveform analysis.
PP, central pulse pressure; Pi, central pressure at the first peak of the central waveform; Ppk, pressure at the second peak of the central waveform; ΔP, augmentation pressure due to reflected wave; Ti round trip time of reflection wave; ED, ejection duration; DTI, diastolic time index; TTI, tension time index.

In healthy people, the reflected wave (Ppk) returns late because the velocity of the aortic pulse wave is low due to the complacency of the arteries. AIx varies from less than zero at age 18 to a value approximating 50% of pulse pressure at the age of 80 years old (Rourke et al., 2010).

It should be noted that AIx is not a simple alternative measure of large arteries stiffness, as it is influenced by several factors that modulate ventricular–vascular coupling. AIx is inversely related to acute changes in HR, which result in a decrease in ejection duration, and a reflected wave that arrives later in the cardiac cycle (Sakuragi & Abhayaratna, 2010). For ease of

comparison for different heart rates, AIx is often normalized to an hear rate of 75 beats/min (Nelson et al., 2010). That index is inversely influenced by body height, left ventricular ejection fraction, peripheral vascular resistance and increases non-linearly with age (Sakuragi & Abhayaratna, 2010).

Contrary to PWV, the positive relation between age and AIx is more prominent in subjects of age less than 50 years, with minimal rise in AIx observed after the age of 65 years (Sakuragi & Abhayaratna, 2010). However, different authors defend that both measures should be complementary rather than interchangeable (Lydakis et al., 2008; Sakuragi & Abhayaratna, 2010; Sharman et al., 2009).

2.2.3 Applanation tonometry

Pulse wave analysis is an essential tool to estimate central haemodynamic parameters (Agnoletti et al., 2014). BP measurement has been used extensively in daily clinical practice to manage cardiovascular disease (Cheng, Lang, Tufanaru, & Pearson, 2013), but it does not provide estimation of central pressures or PWV.

There are two ways to measure CBP, with invasive and non-invasive methods. The gold standard of central BP measurements is aortic root BP, using a saline-filled catheter or an external pressure transducer with tip in situ, but it is not suitable for routine clinical practice (Cheng et al., 2013).

Non-invasive estimation of CBP can be achieved either by using statistical methods relating brachial to CBP or by estimating arterial pressure waveform at the central level, i.e. the ascending aorta or carotid artery (Papaioannou et al., 2009).

Usually, recording of arterial pressure waves is performed by using non-invasive methods, such as applanation tonometry, echo-tracking or plethysmography (Cavalcante et al., 2011; Papaioannou et al., 2009). In order to determine the more reliable measure, in the last decade, several devices have been tested and compared with each other (Cavalcante et al., 2011). According to several studies, applanation tonometry is the most validated method to noninvasively quantify arterial stiffness. It is considered the gold standard index of arterial stiffness (Cavalcante et al., 2011; Nelson et al., 2010; Sakuragi & Abhayaratna, 2010)

This method allows to evaluate the interactions between the left ventricle and the arterial system, providing values of: SBP, DBP, MBP, HR, AIx, ejection fraction and subendocardial

viability (Gusbeth-tatomir & Covic, 2009). Thus, it analyzes the peripheral pulse wave through the influence of physiological or pharmacological stimuli, on central arterial hemodynamics (Dawson et al., 2009; Vlachopoulos, Aznaouridis, & Stefanadis, 2010).

Applanation tonometry records the pulse pressure waveform in the radial artery. This waveform can be analysed by applying a transfer function, and the central pulse pressure waveform in the aorta can be inferred. However, in a recent study it was shown that the transfer function, although required to determine central SBP from the radial artery, is not necessary and that similar information about the central pressure wave can be derived directly from the radial pulse (Gkaliagkousi & Douma, 2009).

In recent years several other techniques, procedures and variables have been proposed for assessing arterial stiffness, however, they are impractical to apply in clinical or too complex which hampers their interpretation (Mitchell et al., 2007; Van Bortel et al., 2012).

2.3 Acute effect of exercise on arterial stiffness

Regular physical exercise has been shown to play an important role in reducing the risk of many chronic diseases (Pal, Radavelli-Bagatini, & Ho, 2013). It causes positive effects on endothelial dysfunction, vascular wall inflammation and arterial stiffness parameters (Laskey, Siddiqi, Wells, & Lueker, 2013; Ribeiro, Alves, Duarte, & Oliveira, 2010)

Physiological response to exercise alters according to the characteristics of the exercise, the subject and the environment (Ruivo & Alcântara, 2012). During aerobic exercise there is an increase in cardiac output in order to improve perfusion of the active muscles. Initially this phenomenon is due to neurohormonal and hydrostatic mechanisms, after that, to an increase at systolic volume and finally to elevation of heart rate. SBP during exercise increases due to increased cardiac output, and the DBP decreases due to reduction in peripheral arterial resistance, in order to improve the perfusion of large muscular groups (Ruivo & Alcântara, 2012).

In resistance training, there is an increase in SBP and DBP due to the exercise pressor reflex. During isometric contractions muscle blood flow is compromised by compression of the vessels (Lydakis et al., 2008). The sudden and large pressure elevations associated with muscular strength training could result in concentric left ventricular hypertrophy and it has impact on the structure and function of the aorta (Kingwell, 2002).

Engage on regular aerobic exercise is one of the most important recommendations to treat hypertension, because it is well known that physical inactivity is a major risk factor for cardiovascular morbidity and mortality, and hypertension contributes to increase this risk (Mancia et al., 2013; Sosner, Gremeaux, Bosquet, & Herpin, 2014). Regular exercise decreases very significantly the risk by up to 60%. The acute BP decrease during exercise and post-exercise changes differ according to the type of exercise (endurance or aerobic and/or strength exercises), however with the repetition of exercise, the chronic hypotensive benefit of physical activity is obtain in both resistance and strength exercises (Sosner et al., 2014). Regarding resistant hypertension, Dimeo et al., (2012) showed that aerobic exercise induces a significant reduction of BP in patients with resistant hypertension. Patients with resistant hypertension have elevated arterial stiffness, more than the controlled hypertension group (Chang, 2014), phenomenon that can be mitigated with exercise.

Per opposition to the chronic effects, the acute effects of exercise seem to be the increase of arterial stiffness (Tartière-Kesri et al., 2012). Unlike aerobic exercise, there are fewer studies evaluating the acute impact of isodynamic exercise on arterial stiffness.

A study involving fifteen healthy subjects assessed arterial stiffness before and immediately after an exercise protocol. The protocol was based on an isometric exercise of the upper limb and dynamic exercise of lower limb. The authors concluded that there was an increase in arterial stiffness in both protocols, being more pronounced in the isometric protocol (Lydakis et al., 2008). More recently, Ribeiro et al. (2014) studied the effects of aerobic exercise, accompanied by upper limb isometric contraction. They showed that this protocol increased derived measures of central pressure and augmentation index, in fourteen healthy male subjects. We intent with this study to add information about the impact of isodynamic exercise reproducing a daily life task on arterial stiffness in patients with resistant hypertension.

CHAPTER 3 – METHODS

3.1 Study design

The study was a quantitative nature and repeated measures design. It was a longitudinal study, because there was an intervention with measurements before and after. There was two groups, an experimental and a control group. The allocation of the participants to the sessions [walk with extra load (10% of total body weight) vs. walk without load] was obtained randomly, what make the study randomized (Fortin, 2009). The study design is depicted in figure 2.

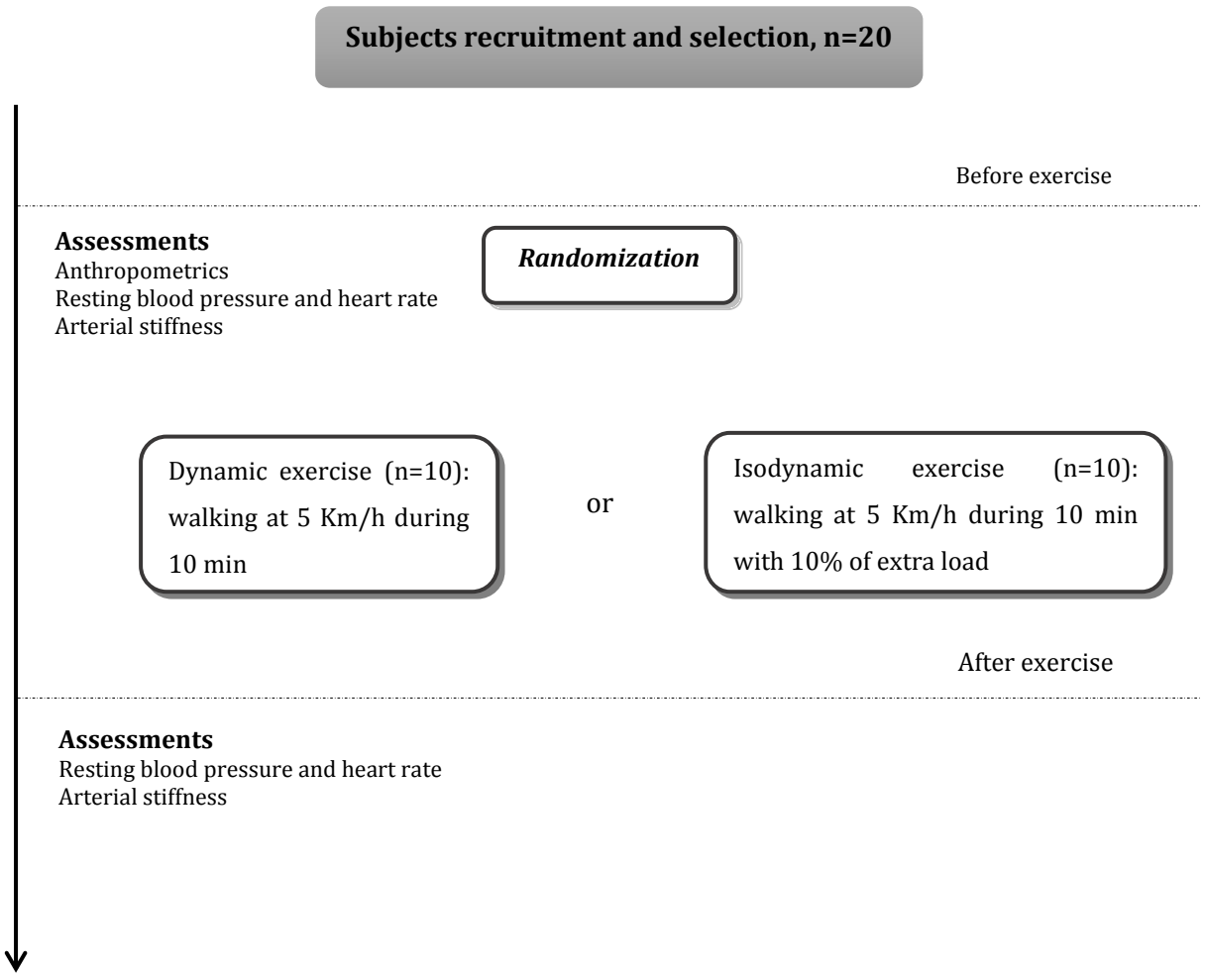

Figure 2- Study design

3.2 Participants

Twenty subjects were recruited in the Consulta Externa de Hipertensão do Serviço de Cardiologia do Centro Hospitalar do Baixo Vouga. The convenience sample was recruited from the database of the Consulta Externa de Hipertensão. Patients were contacted and invite to participate in the study by a cardiologist. Subjects had to satisfy the assumptions of resistant hypertension to be included, BP ≥140/90 mm Hg (or <130/80 mm Hg in patients with diabetes mellitus or chronic kidney disease) in spite of concurrent use of 3 antihypertensive agents of different classes in adequate doses including a diuretic or a BP that is controlled with ≥4 antihypertensive agents (Carey, 2013). Subjects were excluded if they had a regular engagement in physical exercise training in the past 4 weeks before inclusion in the study, symptomatic peripheral arterial occlusive disease, aortic insufficiency or stenosis, hypertrophic obstructive cardiomyopathy, congestive heart failure, uncontrolled cardiac arrhythmia with hemodynamic relevance, signs of acute ischemia in exercise testing, kidney disease, and change of antihypertensive medication in the past 4 weeks.

The ethics committee of Centro Hospitalar do Baixo Vouga, Aveiro, approved the study. All subjects that complied inclusion criteria and accepted to participate received an information sheet with the objectives and study protocol. They were informed that they could leave the study at any time without any penalty or justification. All participants signed an informed consent and all the procedures were conducted according to the declaration of Helsinki (Annex 1).

3.3 Exercise protocol

There were two exercise protocols. Subjects were randomly allocated to each exercise protocol. Randomization was done by choosing a paper containing one of the two options, walk without load vs. walk with additional load. In one exercise protocol, subjects were asked to walk for ten minutes on a treadmill (H/P/Cosmos Quasar 4.0 - Nussdorf, Germany) at a speed of 5Km/h carrying no load. In the other one, they walked in the same treadmill, carrying a load of 10% of their body mass. The load was carried on both upper limbs in two water carboys with handle. Heart rate (HR) and electrocardiogram were continuously monitored during exercise via a telemetric system.

The walking speed of 5 km/h was chosen because it is a comfortably walking speed and this speed has already been tested in a similar protocol (Ribeiro et al., 2014). The duration of the walk and the weight of extra load were set to reproduce a real life situation such as the transport of groceries from supermarket to home.

3.4 Procedures

Assessment of anthropometrics

Initially the examiner weighed and measured the subjects using a standard wall-mounted stadiometer and scale, respectively. Body mass index was calculated from the ratio of weight (Kg) to squared height (m^2).

Assessment of medical history, medication, lipid profile and metabolic parameters

All data regarding medical history were collected from the medical files and validated by patients. They include lipid profile, metabolic parameters, cardiovascular risk factors and medication (including the dosage).

Assessment of resting haemodynamics

After that, subjects sit down during 5 minutes, rested their arm on a table so the brachial artery was levelled with the heart. Resting SBP, DBP and HR were measured using a digital automatic BP monitor (Colin model BP 8800 monitor, Critikron, Inc., Tampa, FL, USA). Two measurements were obtained at intervals of 1 minute and their average recorded. If there was more than 5 mmHg of difference between the two readings, one more reading was obtained for average. The resting rate was monitored for 15s and multiplied by 4 to obtain the resting heart rate for 1 minute. Two readings were conducted at intervals of 1 minute and values were averaged. Peripheral mean BP was determined as DBP + [(SBP-DBP)/3].

Assessment of arterial stiffness-related indexes

Assessment procedures for pulse wave analysis were standardized according to the recommendations (Laurent et al., 2006). All subjects were evaluated in a quiet room. Before sessions, subjects rested seated in a quiet environment for fifteen minutes. Subjects were told

to avoid intense or exhaustive exercise 48 h prior to the beginning and during the study period. No meal or caffeine was allowed within three hours before measurements. Speaking and sleeping were not allowed during measurements. The same well-trained investigator performed all procedures.

Arterial stiffness was measured at baseline (after a period of 15-min rest) and immediately after each exercise session with the carotid-femoral pulse wave velocity and pulse wave analysis using the SphygmoCor system (model SCOR-Px; AtCor Medical, Sydney, Australia). The examiner was experienced and was the only to measure arterial stiffness in all subjects. The reliability index of the evaluator was always above 90%, value given by SphygmoCor System. For PWV analysis the patient was in the supine position in a quiet temperature-controlled room after a brief rest period of at least 5 min and immediately after the exercise bout. Carotid-femoral PWV was determined with the foot-to-foot method using the SphygmoCor System. Consecutive registrations of the carotid and femoral artery pulse waves were electrocardiogram gated and thus the time shift between the appearance of wave at the first and the second sites can be calculated. The distance between the two sites was measured on the body surface to determine carotid-femoral pulse wave velocity in meters/second. The average of measurements over a period of 8s (9-10 cardiac cycles) was calculated. The distance travelled by the pressure wave results from the difference between the surface distances of the recording point at the femoral artery to the sternal notch and the sternal notch to the recording point at the radial artery. PWV is therefore calculated as the distance travelled in meters by the pressure wave divided by the transit time in seconds.

Pulse wave analysis was performed by applanation tonometry (Sphygmocor System, AtCor Medical, Sydney, Australia) of the radial artery in the right wrist with a high-fidelity strain gauge transducer (Millar Instruments, Houston, TX, USA). After 20 sequential waveforms had been acquired and averaged, a validated generalized mathematical transfer function was used to synthesize the corresponding central aortic pressure waveform. Aortic augmentation index and augmentation pressure was derived from this with the technique of pressure waveform analysis. The merging point of the incident and the reflected wave (the inflection point) was then identified on the generated aortic pressure waveform. The parameters generated by this analysis were central pressures, AIx, AIx corrected for heart rate of 75 bpm (AIx@75), and end systolic pressure. AIx denotes the contribution of the wave reflection to the central arterial pressure waveform and is expressed as a percentage of central pulse pressure.

3.5 Data Analysis

After data collection, the SPSS® Statistics 19 (Statistical Package for the Social Sciences version 19) was used to analyze the data. The normality of data distribution was tested with the Shapiro-Wilk test. Data were normally distributed and presented as means ± SD, except PWV that is present as median (Interquartile Range). Baseline, final and change values were compared between groups using independent Chi-squared test, Student t-test or Mann-Whitney Test (PWV). Paired Student t-test were used for within-group comparisons between baseline and post-session in AIx@75 bpm, central and peripheral BP, augmentation pressure, aortic PP, augmentation pressure, end systolic pressure, and heart rate values. Wilcoxon Signed Ranks Test was used for within-group comparisons between baseline and post-session in PWV. $P<0.05$ was considered indicative of statistical significance.

CHAPTER 4 - RESULTS

Baseline characteristics of both groups are presented in **Table 1**. They were statistically similar regarding gender, age, weight and height. Body mass index was the only variable showing significant differences between groups (ρ=0.02).

Table 1 - General characteristics of both groups

Patients Characteristics	***Group without load*** (n=10)	***Group extra-load*** (n=10)	***ρ Value***
General features			
Female, n (%)	6 (60)	3 (30)	0.2
Male, n (%)	4 (40)	7 (70)	
Age (years)	61.60 ± 8.6	55.60 ± 8.3	0.13
Weight (Kg)	88.0 ± 11.2	82.9 ± 9.2	0.28
Height (cm)	163.5 ± 4.2	169.5 ± 8.5	0.62
Body mass index, Kg/m²	32.9 ± 4.4	28.8 ± 2.2	0.02
Medication (%)			
β-blockers	80%	50%	
ACE inhibitors	60%	40%	
Diuretics	60%	90%	
Angiotensin- receptor blockers	40%	40%	
Anticoagulants	10%	0%	
Calcium Channel blockers	60%	80%	
Vasodilator	20%	-	
Midazoline receptors blockers	40%	30%	
Statins	30%	50%	
Other medications	50%	40%	
Concomitant diseases (%)			
Diabetes mellitus	30%	-	

At rest (e.g. before exercise sessions), there were no significant differences between groups regarding HR, SAP, DAP, mean pressure, PP, aortic SP, aortic DP, aortic mean pressure, aortic PP, AP, AIx@75, end systolic pressure, and PWV (ρ= 0.18) (**Table 2)**.

Table 2 - Comparisons at baseline between groups in arterial stiffness-related indexes, heart rate and blood pressure

	GROUP WITHOUT LOAD	GROUP EXTRA-LOAD	P VALUE
HR (bpm)	69.0 ± 9.3	69.1 ± 12.2	0.98
SAP (office) (mmHg)	163.8 ± 24.2	161.1 ± 19.2	0.79
DAP (office) (mmHg)	85.7 ± 11.9	93.7 ± 14.3	0.19
MEAN P (mmHg)	114. ± 14.9	115.5 ± 19.1	0.85
PP (mmHg)	78.1 ± 20.8	69.5 ± 14.2	0.29
AORTIC SP (mmHg)	151.4 ± 25.0	147.9 ± 20.9	0.74
AORTIC DP (mmHg)	87.1 ± 12.0	92.7 ± 17.5	0.42
AORTIC MEAN P (mmHg)	114.0 ± 14.9	115.5 ± 19.1	0.85
AORTIC PP (mmHg)	64.3 ± 21.6	55.2 ± 13.9	0.28
AP (mmHg)	20.7 ± 11.8	14.7 ± 7.7	0.19
AIX@75 (%)	27.7 ± 8.3	24.0 ± 10.6	0.40
END SYSTOLIC PRESSURE (mmHg)	131.6 ±19.1	131.1 ± 19.9	0.95
PWV‡ (m/s)	8.4 (0.7)	7.9 (2.0)	0.18

HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; Mean p: mean pressure; PP: pulse pressure; Aortic SP: aortic systolic pressure; Aortic DP: aortic diastolic pressure; AP: augmentation pressure; AIx: augmentation index; PWV: pulse wave velocity. ‡ Values are median (Interquartile Range).

SAP, PP and aortic PP increased significantly in both groups after the exercise protocol, on the other hand DAP decreased significantly also in both groups after the exercise protocol **(table 3).** The changes in these parameters were not significantly different between groups **(table 3).** In the group without load, the exercise session decreased significantly aortic DP and increased significantly AP **(table 3)**. Nonetheless, the mean change in this group was not different from the group with extra-load **(table 3)**. To note, that it was not possible to measure PWV in 6 subjects (4 in the group without load

Table 3 - Comparison of peripheral and derived central hemodynamic parameters assessed after the exercise sessions

PARAMETER	GROUP WITHOUT LOAD		GROUP EXTRA-LOAD		95% CONFIDENCE INTERVAL OF DIFFERENCE
	Post exercise	Change	Post exercise	Change	
HR (bpm)	70.6 ± 9.1	1.6 ± 3.7	71.6 ± 12.3	2.5 ± 3.7	0.9 (-2.6 – 4.3)
SAP (mmHg)	171.0 ± 27.2*	7.2 ± 2.9	174.4 ±13.1*	13.3 ± 14.9	6.1 (-5.5 – 17.7)
DAP (mmHg)	72.5 ± 8.9*	-13.2 ±11.3	84.0 ±17.8*	-9.7 ± 12.5	3.5 (-7.7 – 14.7)
MEAN P (mmHg)	110.3 ± 13.3	-3.7 ± 9.0	116.1 ± 15.0	0.6 ± 11.4	4.3 (-5.4 – 14.0)
PP (mmHg)	99.5 ± 24.3*	21.4 ± 13.4	90.4 ± 19.5*	20.9 ± 17.6	-0.5 (-15.2 – 14.2)
AORTIC SP (mmHg)	158.2 ± 26.8	6.8 ± 12.5	155.7 ± 13.2	7.8 ± 11.4	1.0 (-10.3 – 12.3)
AORTIC DP (mmHg)	74.3 ± 8.7*	-12.8 ± 11.0	86.1 ± 18.0	-6.6 ± 13.3	6.2 (-5.3 – 17.7)
AORTIC MEAN P (mmHg)	110.3 ± 13.3	-3.7 ± 9.0	116.1 ± 15.0	0.6 ± 11.4	4.3 (-5.4 – 14.0)
AORTIC PP (mmHg)	83.9 ±24.6*	19.6 ± 13.9	69.6 ±16.5*	14.4 ± 13.3	-5.2 (-18.0 – 7.6)
AP (mmHg)	25.9 ± 12.3*	5.2 ± 4.0	17.6 ± 6.7	2.9 ± 5.8	-2.3 (-7.0 – 2.4)
AIX@75 (%)	28.8 ± 7.6	1.1 ± 2.1	25.2 ± 6.9	1.2 ± 6.6	0.1 (-4.8 – 5.0)
END SYSTOLIC PRESSURE (mmHg)	131.9 ± 20.0	0.9 ±10.2	134.1 ± 14.2	3.0 ± 11.5	2.1 (-8.5 – 12.7)
PWV‡ (m/s)	8.5 (2.6)	0.15 (1.6)	8.2 (2.2)	0.10 (1.7)	-0.4 (0.3 – - 1.3)

HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; Mean p: mean pressure; PP: pulse pressure; Aortic SP: aortic systolic pressure; Aortic DP: aortic diastolic pressure; AP: augmentation pressure; AIx: augmentation index; PWV: pulse wave velocity. ‡ Values are median (Interquartile Range). * significantly different from baseline, $p<0.05$

CHAPTER 5 – DISCUSSION

The main purpose of the present study was to evaluate the impact of an isodynamic exercise on arterial stiffness-related indexes in subjects with RH. The results showed that there are no significant changes in arterial stiffness with isodynamic exercise. The arterial stiffness parameters did not vary significantly between groups.

Is well known the importance of arterial stiffness in cardiovascular disease (Gusbeth-tatomir & Covic, 2009; Kingwell, 2002; Vlachopoulos et al., 2010). After conducting several studies it was shown that the gold standard method for assessing, non-invasively, arterial stiffness is the measurement of PWV (Mancia et al., 2013).

In this study, PWV was used as a way of accessing the stiffness of the arteries. Values at baseline were already slightly elevated in both groups, median of 8.4 (0.7) in the group without load and 7.9 (2.0) in the group with extra-load. Reference values in normal adults of middle-age are 4 m/s in the ascending aorta, 5 m/s in the abdominal aorta and carotids, 7 m/s in the brachial artery, and 8 m/s in the iliac arteries (Zambanini et al., 2005).

It was not possible to measure central PWV in all subjects (n=6). This is related to a limitation of applanation tonometry, which is difficult to use in obese patients (Boutouyrie, Revera, & Parati, 2009). Most of the subjects that we cannot evaluate belonged to the group without load (n=4).

Increasing values of SBP, PP and aortic PP, in response to exercise, are related to adaptive responses in the cardiovascular system, particularly with increased sympathetic nervous system activity. During exercise, the concentration of circulating catecholamines increases, causing increased tension developed by the smooth muscle cells and may cause a rise in arterial stiffness by increased resistance to blood flow and hence a greater speed of retrograde wave (Yoon et al., 2010).

Tartière-Kesri et al. (2012) shown that a single bout of aerobic exercise of moderate intensity increased proximal AS, in patients with CVD. In this specific population, maximal exercise capacity is reduced because it is related with AS and consequently with maximum cardiac output (Kingwell, 2002). Likewise Kingwell (2002) reported an inverse correlation between time to ischemia, during treadmill exercise and arterial stiffness in coronary artery disease. This phenomenon is maximized in patients with RH, due to the increased stiffness of arteries (Chang, 2014). Thus, in this study it was chosen a load of 10% of the total body weight, which could represent significant exercise intensity for this population. It could be supposed that for

higher intensity and load, haemodynamics parameters like carotid SBP, BP, PP and PP amplification, would rise. However, the main aim was to recreate an activity of daily living.

There are few studies about the effect of exercise on patients with RH; moreover, there are no studies about the impact of isodynamic exercise on stiffness of arteries in these patients. Dimeo et al. (2012) studied the effect of aerobic exercise in resistant hypertension, and they concluded that regular exercise reduced BP on exertion, however arterial compliance and cardiac index remained unchanged. Another study showed that during all types of acute stress (including dynamic exercise) estimated central arterial stiffness increased (Lydakis et al., 2008). The results of the present study are different, nonetheless cannot be forgotten that this sample composed by patients with resistance hypertension.

More recently, a study with fourteen healthy subjects (age 31.0 ± 1.0 years) showed that walking with an additional load of 10% of their body weight (aerobic exercise combined with upper limb isometric contraction) increases derived measures of central pressure and augmentation index, an index of wave reflection and arterial stiffness (Ribeiro et al., 2014). However, the same protocol applied to the population of this study, did not achieve the same results. Two main differences exist between this study and the study of Ribeiro et al; first, the subjects were younger and free of disease. Our study population was older, indicating that they would have less compliant arteries. With increasing age the stiffness of arteries increases, which also happens in people with resistant hypertension. Both factors associated could lead to an increase in arterial stiffness and central pressure after exercise with extra load, nonetheless this did not happen in the present study. Perhaps, the intensity and/or duration of the exercise together with the medication were not enough to induce changes in arterial stiffness, even in these patients.

The results of the present study need to be confirmed in future research in order to provide more insight to help physiotherapists and other professionals prescribing exercise safely for patients with resistant hypertension. Based on our data, one could affirm that isodynamic exercise can be incorporated into daily life activities, such as walking while carrying a load on the upper limbs, without increasing the risk of a cardiovascular event. In this kind of population, although increasing afterload, the indexes of arterial stiffness were not significantly increased. It is noteworthy that these results were obtained with this specific protocol, in order to exemplify the activities of daily life.

Limitations of the study and future work

To our knowledge, this was the first study with this aim conducted in patients with resistant hypertension. However, it should be interpreted within the context of its limitations. The biggest limitation is the sample size, however we have to take into account that resistant hypertension represents only a portion of the population with hypertension.

The two sessions were not held at similar time of the day, and it is recommend, especially in studies with repeated measurements, since central hemodynamics present a circadian variation (Papaioannou et al., 2009). However, we were constrained by the availability and the operating hours of the hospital. Another limitation is the study design, which was not a crossover design. Despite not having differences at baseline, it is recommended that future studies use a crossover design with all the participants performing the two sessions.

Another limitation arises from the fact that in 6 patients it was not possible to assess PWV. This could have influenced PWV results.

Patients with resistant hypertension are at high risk for adverse cardiovascular events (Dimeo et al., 2012). There are few data on the effects of different types of exercise on arterial stiffness of these patients. Further studies with larger samples and different exercise protocols are necessary, in order to safely prescribe exercise and choose the most suitable type of exercise for patients with resistance hypertension.

CHAPTER 6 – CONCLUSION

In conclusion, this study shows that a daily life activity combining dynamic and isometric exercise, such as walking while carrying a load on the upper limbs, does not induce any change on arterial stiffness, derived measures of central pressure and AIx, an index of wave reflection and arterial stiffness, assessed by applanation tonometry in patients with resistant hypertension.

This study adds data to help the physiotherapists to prescribe exercise safely for patients with resistant hypertension. It suggests that the isodynamic exercise could be incorporated into daily life activities, such as walking while carrying a load on the upper limbs, without increasing the risk of a cardiovascular event. This is a matter of interest, because cardiovascular diseases are increasing and resistant hypertension is part of this group, and safe and effective strategies are necessary for the treatment of this condition.

REFERENCES

Agnoletti, D., Millasseau, S. C., Topouchian, J., Zhang, Y., Safar, M. E., & Blacher, J. (2014). Pulse wave analysis with two tonometric devices: a comparison study. *Physiological Measurement*, *35*(9), 1837–48.

Bautista, L. E. (2003). Inflammation, endothelial dysfunction, and the risk of high blood pressure: epidemiologic and biological evidence. *Journal of Human Hypertension*, *17*(4), 223–30.

Boutouyrie, P., Revera, M., & Parati, G. (2009). Obtaining arterial stiffness indices from simple arm cuff measurements: the holy grail? *Journal of Hypertension*, *27*(11), 2159–61.

Calhoun, D. a, Jones, D., Textor, S., Goff, D. C., Murphy, T. P., Toto, R. D., … Carey, R. M. (2008). Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension*, *51*(6), 1403–19.

Carey, R. M. (2013). Resistant hypertension. *Hypertension*, *61*(4), 746–50.

Cavalcante, J. L., Lima, J. a C., Redheuil, A., & Al-Mallah, M. H. (2011). Aortic stiffness: current understanding and future directions. *Journal of the American College of Cardiology*, *57*(14), 1511–22.

Cecelja, M., & Chowienczyk, P. (2012). Role of arterial stiffness in cardiovascular disease. *JRSM Cardiovascular Disease*, *1*(4).

Chang, J. (2014). Relationship between resistant hypertension and arterial stiffness assessed by brachial-ankle pulse wave velocity in the older patient, *Clinical Interventions in Aging,9,* 1495–1502.

Cheng, H.-M., Lang, D., Tufanaru, C., & Pearson, A. (2013). Measurement accuracy of non-invasively obtained central blood pressure by applanation tonometry: a systematic review and meta-analysis. *International Journal of Cardiology*, *167*(5), 1867–76.

Cortez-Dias, Susana Martins, Adriana Belo, M. F. (2009). Prevalência e Padrões de Tratamento da Hipertensão Arterial nos Cuidados. *Revista Portuguesa de Cardiologia : Orgão Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology : An Official Journal of the Portuguese Society of Cardiology*, *28*(September 2008), 499–523.

Dawson, E. a, Black, M. a, Pybis, J., Cable, N. T., & Green, D. J. (2009). The impact of exercise on derived measures of central pressure and augmentation index obtained from the SphygmoCor device. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *106*(6), 1896–901.

Dimeo, F., Pagonas, N., Seibert, F., Arndt, R., Zidek, W., & Westhoff, T. H. (2012). Aerobic exercise reduces blood pressure in resistant hypertension. *Hypertension*, *60*(3), 653–8.

Fagard, R. H. (2012). Resistant hypertension. *Heart (British Cardiac Society)*, *98*(3), 254–61.

Fortin, M.-F. (2009). *Fundamentos e etapas do processo de Investigação*. (Lusodidacta, Ed.). Loures.

Gkaliagkousi, E., & Douma, S. (2009). The pathogenesis of arterial stiffness and its prognostic value in essential hypertension and cardiovascular diseases. *Hippokratia*, *13*(2), 70–75.

Gusbeth-tatomir, P., & Covic, A. (2009). What is new in arterial stiffness. *Mædica - a Journal of Clinical Medicine*, *4*(1), 12–16.

Guyton, A.C. & Hall, J. . (2002). *Tratado De Fisiologia Médica*. (E. Rj, Ed.) (10th ed., pp. 144–151). Guanabara Koogan.

Hamilton, P. K., Lockhart, C. J., Quinn, C. E., & McVeigh, G. E. (2007). Arterial stiffness: clinical relevance, measurement and treatment. *Clinical Science (London, England : 1979)*, *113*(4), 157–70.

Kingwell, B. A. (2002). Proceedings of the Australian Physiological and Pharmacological Society Symposium : Integrative Physiology of Exercise- large artery stiffness : implications for exercise capacity and cardiovascular risk. *Clinical and Experimental Pharmacology and Physiology*, *29*(July 2001), 214–217.

Kinlay, S., Creager, M. a., Fukumoto, M., Hikita, H., Fang, J. C., Selwyn, a. P., & Ganz, P. (2001). Endothelium-Derived Nitric Oxide Regulates Arterial Elasticity in Human Arteries In Vivo. *Hypertension*, *38*(5), 1049–1053.

Kumar, N., Calhoun, D. a, & Dudenbostel, T. (2013). Management of patients with resistant hypertension: current treatment options. *Integrated Blood Pressure Control*, *6*, 139–51.

Laskey, W., Siddiqi, S., Wells, C., & Lueker, R. (2013). Improvement in arterial stiffness following cardiac rehabilitation. *International Journal of Cardiology*, *167*(6), 2734–8.

Laurent, S., Cockcroft, J., Van Bortel, L., Boutouyrie, P., Giannattasio, C., Hayoz, D., … Struijker-Boudier, H. (2006). Expert consensus document on arterial stiffness: methodological issues and clinical applications. *European Heart Journal*, *27*(21), 2588–605. doi:10.1093/eurheartj/ehl254

Lydakis, C., Momen, a, Blaha, C., Gugoff, S., Gray, K., Herr, M., … Sinoway, L. I. (2008). Changes of central haemodynamic parameters during mental stress and acute bouts of static and dynamic exercise. *Journal of Human Hypertension*, *22*(5), 320–8.

Mancia, G., Fagard, R., Narkiewicz, K., Redon, J., Zanchetti, A., Böhm, M., … Wood, D. a. (2013). 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *European Heart Journal*, *34*(28), 2159–219.

Mitchell, G. F., Guo, C.-Y., Kathiresan, S., Vasan, R. S., Larson, M. G., Vita, J. a, … Benjamin, E. J. (2007). Vascular stiffness and genetic variation at the endothelial nitric oxide synthase locus: the Framingham Heart study. *Hypertension*, *49*(6), 1285–90.

Montero, D., Roche, E., & Martinez-Rodriguez, A. (2014). The impact of aerobic exercise training on arterial stiffness in pre- and hypertensive subjects: a systematic review and meta-analysis. *International Journal of Cardiology*, *173*(3), 361–8.

Nelson, M. R., Stepanek, J., Cevette, M., Covalciuc, M., Hurst, R. T., & Tajik, A. J. (2010). Noninvasive measurement of central vascular pressures with arterial tonometry: clinical revival of the pulse pressure waveform? *Mayo Clinic Proceedings*, *85*(5), 460–72.

Paiva, L., Cachulo, M. C., Providencia, R., Barra, S., Dinis, P., & Leitao-Marques, A. (2012). Overview of resistant hypertension: A glimpse of the cardiologist's current standpoint. *World Journal of Cardiology*, *4*(9), 275–83.

Paiva, S., Complementar, I., & Geral, D. C. (2005). Abordagem da hipertensão. *Revista Portuguesa de Clinica Geral*, *21*, 461–467.

Pal, S., Radavelli-Bagatini, S., & Ho, S. (2013). Potential benefits of exercise on blood pressure and vascular function. *Journal of the American Society of Hypertension : JASH*, *7*(6), 494–506.

Papaioannou, T. G., Protogerou, A. D., Stamatelopoulos, K. S., Vavuranakis, M., & Stefanadis, C. (2009). Non-Invasive Methods and Techniques for Central Blood Pressure Estima- tion : Procedures , Validation , Reproducibility and Limitations. *Current Pharmaceutical Design*, *15*(3), 245–253.

Patvardhan, E., Heffernan, K. S., Ruan, J., Hession, M., Warner, P., Karas, R. H., & Kuvin, J. T. (2011). Augmentation index derived from peripheral arterial tonometry correlates with cardiovascular risk factors. *Cardiology Research and Practice*, *2011*, 253758.

Pimenta, E., & Calhoun, D. a. (2012). Resistant hypertension: incidence, prevalence, and prognosis. *Circulation*, *125*(13), 1594–6.

Quinn, U., Tomlinson, L. a, & Cockcroft, J. R. (2012). Arterial stiffness. *JRSM Cardiovascular Disease*, *1*(6).

Ribeiro, F., Alves, A. J., Duarte, J. A., & Oliveira, J. (2010). Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *International Journal of Cardiology*, *141*(3), 214–21.

Ribeiro, F., Oliveira, N. L., Pires, J., Alves, A. J., & Oliveira, J. (2014). Treadmill walking with load carriage increases aortic pressure wave reflection. *Revista Portuguesa de Cardiologia : Orgão Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology : An Official Journal of the Portuguese Society of Cardiology*, *33*(7-8), 425–30.

Rocha, E. (2011). Velocidade da onda de pulso arterial: um marcador da rigidez arterial e a sua aplicabilidade na prática clínica. *Revista Portuguesa de Cardiologia : Orgão Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology : An Official Journal of the Portuguese Society of Cardiology*, *30*(9), 699–702.

Roman, M. J., Devereux, R. B., Kizer, J. R., Okin, P. M., Lee, E. T., Wang, W., … Howard, B. V. (2009). High central pulse pressure is independently associated with adverse cardiovascular outcome the strong heart study. *Journal of the American College of Cardiology*, *54*(18), 1730–4.

Rourke, M. F. O., Staessen, J. A., Vlachopoulos, C., Duprez, D., & Plante, E. (2010). Clinical Applications of Arterial Stiffness ; Definitions and Reference Values, 426–444.

Ruivo, J. a, & Alcântara, P. (2012). [Hypertension and exercise]. *Revista Portuguesa de Cardiologia : Orgão Oficial Da Sociedade Portuguesa de Cardiologia = Portuguese Journal of Cardiology : An Official Journal of the Portuguese Society of Cardiology*, *31*(2), 151–8.

Sakuragi, S., & Abhayaratna, W. P. (2010). Arterial stiffness: methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. *International Journal of Cardiology*, *138*(2), 112–8.

Sharman, J. E., Davies, J. E., Jenkins, C., & Marwick, T. H. (2009). Augmentation index, left ventricular contractility, and wave reflection. *Hypertension*, *54*(5), 1099–105.

Sosner, P., Gremeaux, V., Bosquet, L., & Herpin, D. (2014). [High blood pressure and physical exercise]. *Annales de Cardiologie et D'angéiologie*, *63*(3), 197–203.

Tartière-Kesri, L., Tartière, J.-M., Logeart, D., Beauvais, F., & Cohen Solal, A. (2012). Increased proximal arterial stiffness and cardiac response with moderate exercise in patients with heart failure and preserved ejection fraction. *Journal of the American College of Cardiology*, *59*(5), 455–61.

Van Bortel, L. M., Laurent, S., Boutouyrie, P., Chowienczyk, P., Cruickshank, J. K., De Backer, T., … Weber, T. (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *Journal of Hypertension*, *30*(3), 445–8.

Vlachopoulos, C., Aznaouridis, K., & Stefanadis, C. (2010). Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. *Journal of the American College of Cardiology*, *55*(13), 1318–27.

Yoon, E. S., Jung, S. J., Cheun, S. K., Oh, Y. S., Kim, S. H., & Jae, S. Y. (2010). Effects of acute resistance exercise on arterial stiffness in young men. *Korean Circulation Journal*, *40*(1), 16–22.

Zambanini, a, Cunningham, S. L., Parker, K. H., Khir, a W., McG Thom, S. a, & Hughes, a D. (2005). Wave-energy patterns in carotid, brachial, and radial arteries: a noninvasive approach using wave-intensity analysis. *American Journal of Physiology. Heart and Circulatory Physiology*, *289*(1), H270–6.

ANNEX

Annex I

Informed Consent

universidade de aveiro

Folha de Informação ao Utente

Impacto do exercício isodinâmico reproduzindo uma tarefa da vida diária, na rigidez arterial, em indivíduos com hipertensão arterial refratária.

Está a ser realizado um estudo de investigação clínica que pretende melhorar os resultados para a saúde dos utentes. Neste contexto, a relevância da participação dos envolvidos é fundamental para os resultados do estudo. Assim, vimos convidá-lo(a) a participar nesta pesquisa. Mas antes de decidir participar ou não, é importante que compreenda porque é que a investigação está a ser realizada e o que é que a mesma envolve. Por isso lhe pedimos que leia a informação com atenção e converse sobre a sua participação com outras pessoas, se assim o entender. Se houver algum aspecto que não esteja claro para si ou se precisar de mais informação, por favor pergunte aos investigadores (contactos no final deste documento). Use o tempo que precisar para decidir se deseja ou não participar.
Muito obrigada, desde já, pela sua atenção.

Qual é o propósito do estudo?
O presente estudo foi desenvolvido para avaliar os efeitos da marcha na passadeira, com carga, na rigidez arterial (exercícios aeróbios com contrações isométricas dos membros superiores) em indivíduos com hipertensão arterial refratária.

Perguntas mais frequentes:

Porque é que fui escolhido?
Foi escolhido/a porque está registado na base de dados da consulta externa de hipertensão do serviço de cardiologia do Hospital de Aveiro. Para este estudo precisamos de analisar dados de pessoas, com uma condição clínica semelhante à sua, desde que aceitem participar.

Tenho de participar?
A decisão de participar, ou não, é completamente sua. Se decidir participar vamos pedir-lhe que leia e assine um formulário de consentimento informado, mas é totalmente livre de

desistir a qualquer momento, sem que para tal tenha de dar qualquer justificação. A decisão de desistir ou de não participar, não afectará a qualidade dos serviços de saúde que lhe são prestados agora ou no futuro, nem implicará qualquer outra consequência para si.

O que me acontecerá caso decida participar?

Se decidir participar, por favor diga-o ao seu médico, fisioterapeuta ou enfermeiro ou a um dos investigadores, cujos contactos estão no final deste documento. O investigador irá ao seu encontro e pedir-lhe-á que leia e assine o formulário de consentimento informado, entregando-lhe uma cópia deste documento, e tendo em conta a sua disponibilidade, combinará uma data para a avaliação.

Caso sinta que não consegue realizar alguma das tarefas, pode declarar o mesmo a qualquer momento e a tarefa será terminada sem qualquer consequência para si.

Nenhum destes testes provoca qualquer desconforto. No entanto, se decidir não participar neste estudo, nenhum serviço que lhe é habitualmente prestado será afectado.

O que tenho de fazer?

Não tem de fazer nada de especial. Apenas lhe solicitamos que compareça no horário combinado para preenchimento do Questionário de Atividade Física e para a realização da marcha numa passadeira. Os horários exactos ser-lhe-ão comunicados pelo investigador e as sessões realizar-se-ão no Hospital de Aveiro/Universidade de Aveiro onde está a ser acompanhado.

Quais são os efeitos secundários de qualquer tratamento que eu vá receber quando participar?

Não existem efeitos secundários

Quais são as possíveis desvantagens e riscos se eu resolver participar?

Não existem quaisquer desvantagens de participar no estudo. No entanto, se tiver alguma preocupação, por favor contacte os investigadores para se esclarecer

Quais são os possíveis benefícios se eu resolver participar?

Não existem benefícios directos de participar no estudo. No entanto, ficará mais bem informado sobre o seu problema e sobre possíveis tratamentos. Para além disso, a

informação que se obterá através deste estudo poderá ajudar a desenvolver intervenções mais completas para avaliar e tratar outros utentes que sofrem de hipertensão refratária.

A minha participação será confidencial?

Toda a informação recolhida no decurso do estudo será mantida estritamente confidencial. Os dados recolhidos no computador não serão gravados com o seu nome, mas sim com um código, para que ninguém o/a possa identificar, e o computador será protegido com uma palavra-chave. Apenas os investigadores do projecto terão acesso aos seus dados.

O que acontecerá aos resultados do estudo?

Os resultados do estudo serão analisados e incorporados em Dissertações de Mestrado e Teses de Doutoramento e alguns serão publicados em Revistas Científicas. No entanto, em nenhum momento o participante será identificado. Se gostar de obter uma cópia de qualquer relatório ou publicação, por favor diga ao investigador com quem contactar.

Contactos para mais informações sobre o estudo

Se quiser obter mais informações sobre o estudo, pode telefonar ou escrever para:

Nádia Almeida
Escola Superior de Saúde da Universidade de Aveiro,
Universidade de Aveiro,
Campus de Santiago,
Edifício III, 3810- 193, Aveiro
Telefone: 939484537
e-mail: nadia@ua.pt

Muito obrigada por ter lido esta informação.

Código_____

Consentimento informado

Eu concordo em participar no estudo sobre *o Impacto do exercício isométrico reproduzindo uma tarefa da diária, na rigidez arterial em indivíduos com hipertensão arterial refratária*.
Confirmo que **percebi a informação** que me foi dada e tive a **oportunidade de questionar** e de me esclarecer.
Percebo que a minha **participação é voluntária** e que sou **livre de desistir**, em qualquer altura, sem dar nenhuma explicação, sem que isso afecte qualquer serviço de saúde e social que me é prestado.
Compreendo que os **dados** recolhidos durante o estudo são **confidenciais** e só os alunos e docente da Universidade de Aveiro têm acesso a eles. E dou portanto, autorização para que os mesmos tenham acesso a esses dados.
Aceito que os resultados do estudo sejam publicados em Revistas Científicas e usados noutras investigações, sem que haja qualquer quebra de confidencialidade. E dou portanto, autorização para a **utilização dos dados** para esses fins.

_____	_____	_____
Nome do utente	Data	Assinatura

_____	_____	_____
Investigador/a	Data	Assinatura